α-Diethylaminomethyl-2-β-naphthyl-4-quinolinemethanol.—To the reaction mixture (0.0365 mole oxide, 10 ml. of diethylamine, sixteen hours) after excess diethylamine was removed by distillation were added 75 ml. of ethanol and 10 g. of phosphoric acid in 20 ml. of ethanol. The separated crystals were recrystallized from aqueous alcohol to yield 10.0 g. (57%) of monophosphate monohydrate, m. p. 190–194°.

α-Dibutylaminomethyl-2-ethoxy-4-quinolinemethanol.—The reaction mixture (0.075 mole oxide, 0.075 mole dibutylamine, nine hours) was freed of dibutylamine by steam-distillation. Then cooling and scratching the residual oil induced crystallization. Recrystallization from ligroin (b. p. 30–70°) yielded 16.0 g. (60%) of material, m. p. 40–43°. Two further recrystallizations produced the analytical sample, m. p. 40–42°.

Warming with aqueous hydrochloric acid converted the material to another compound, m. p. 133–134°, with a 2-hydroxy instead of ethoxy group.

α-Dibutylaminomethyl-2-amino-4-quinolinemethanol.—From the reaction mixture (0.0495 mole 2-acetamido-4-quinolyl ethylene oxide, 1100 ml. of anh. dibutylamine, sixty-eight hours) most of the excess dibutylamine was removed by distillation at reduced pressure and the rest by distillation from 250 ml. of 3 *N* sodium hydroxide solution. The remaining viscous oil was rinsed several times with water and dried *in vacuo* over concd. sulfuric acid. The dried oil was dissolved by warming in 120 ml. of cyclohexane. Cooling yielded 13.6 g. of material, m. p. 80.2–82.4°, probably not completely deacetylated.

The pure aminoalcohol was isolated by refluxing 15.0 g. of the above mixture with 150 ml. of 6 *N* sodium hydroxide solution and 100 ml. of 95% ethanol for three hours. Then 200 ml. of water was added and the mixture extracted three times with ether. The ether solution was washed with water and dried over potassium carbonate. The ether was removed and the resultant viscous oil was taken up in 25 ml. of cyclohexane. Cooling yielded 9.6 g., m. p. 84.2–85.0°. A second crop of 2.0 g. was isolated from the mother liquor to give an over-all yield from the oxide of 73%.

α-Diethylaminomethyl-2-phenylthio-4-quinolinemethanol.—From the oxide ring opening (oxide from 0.0050 mole of crude bromohydrin hydrochloride, 15 ml. of diethylamine, 15 hours) was obtained, after recrystallization from ethanol-ether, the aminoalcohol dihydrochloride, m. p. 196–200° (dec.), in 80% yield.

The reaction of bromohydrin hydrochloride with excess diethylamine for a 24-hour reflux period gave rise to the same product, m. p. 200–204° (dec.), in 43% yield.

α-Diethanolaminomethyl-2-*p*-chlorophenyl-6,8-dichloro-4-quinolinemethanol.—The crude product (0.0223 mole oxide, 150 ml. of redistilled diethanolamine, 20 hours) was dried over sodium hydroxide *in vacuo*. An unidentified oily impurity was removed by triturating the crude material with 60 ml. of hot ethyl acetate. After cooling, there was obtained 5.64 g. (56%) of aminoalcohol, m. p. 162–165°. Recrystallization from ethanol yielded 4.72 g. (46.5%) of colorless leaves, m. p. 164–166°.

1-(2-Ureido-4-quinolyl)-2-dibutylaminoethyl Carbamate.—A mixture of 3.9 g. (0.0124 mole) of α-dibutylaminomethyl-2-amino-4-quinolinemethanol, 1.30 g. (0.0124 mole) of nitrourea and 45 ml. of anhydrous dioxane was heated until the vigorous evolution of gas began and then refluxed a half hour after it subsided. Two more 1.30-g. portions of nitrourea were added at half-hour intervals and the mixture was refluxed forty-five minutes after the last addition.

The dioxane was removed on a steam-bath at reduced pressure leaving a viscous brown oil which crystallized on cooling. This material was triturated with 40 ml. of benzene and the solid isolated by centrifuging, the liquid layer being saved for recovery of starting material. Recrystallization from benzene–isopropanol gave 1.45 g. (28%) of material, m. p. 158.5–162.3°, and a second crop of 0.25 g. (5%).

Starting material was recovered by removal of solvent from the trituration mother liquor, refluxing the resultant oil three hours with alcoholic sodium hydroxide solution, extraction with ether and crystallization from cyclohexane. This yielded 0.70 g. (18%) of α-dibutylaminomethyl-2-amino-4-quinolinemethanol. The yield of product was 1.70 g. (50%, allowing for recovered starting material).

A small sample was recrystallized twice from benzene–isopropanol; m. p. 165.4–166.0°.

Summary

A series of α-dialkylaminomethyl-4-quinolinemethanols with various substituents in the 2-position of the quinoline nucleus has been synthesized.

The ethanolamines were derived from the corresponding 4-aceto- and 4-bromoacetoquinolines prepared from the appropriate 2-substituted cinchoninic acids or esters. Reduction of the haloketones to halohydrins and conversion of the latter to ethylene oxides proceeds satisfactorily. Opening of the oxide ring with dialkyl amine gave rise to the desired aminoalcohols.

LOS ANGELES 24, CALIF. RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Studies in the Quinoline Series. II. The Preparation of Some Dialkylaminomethyl-4-quinoline Methanols[1,2]

BY KENNETH N. CAMPBELL AND JAMES F. KERWIN[3,4]

As part of the extensive antimalarial research program carried out in this country during the war, it seemed desirable to prepare dialkylaminomethylquinoline methanols of various types; in this paper are recorded some of those with the side chain attached to the 4-position of the quinoline ring, and with methoxyl, chlorine or hydrogen attached at the 6-position, 1.

Rabe[5] and Kaufmann[6] made a few compounds of this type some years ago, with dimethylamino, diethylamino and piperidino groups; more recently King and Work[7] prepared an extensive series. Other workers under the auspices of the

(1) Previous paper in this series: Campbell and Schaffner, THIS JOURNAL, **67**, 86 (1945).

(2) The work reported here was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Notre Dame.

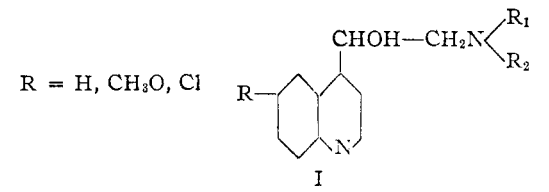
(3) A part of this material is abstracted from the Ph.D. dissertation of James F. Kerwin, June, 1944.

(4) Present address: Smith, Kline and French Laboratories, Philadelphia, Pennsylvania.

(5) Rabe, Pasternack and Kindler, *Ber.*, **50**, 144 (1916).

(6) Kaufmann, *ibid.*, **46**, 1831 (1913).

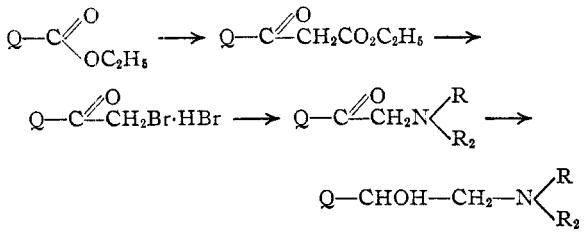
(7) King and Work, *J. Chem. Soc.*, 1307 (1940); 401 (1942).



I

Committee on Medical Research, especially Lutz,[8] Jacobs,[9a] and Buchman[9b] and their co-workers, have made compounds of this type also.

The methods used in the present work were in general similar to those used by the earlier workers, except that improved procedures were developed for many of the steps. The ethyl cinchoninates were converted by the Claisen condensation into the corresponding ethyl 4-quinoloylacetates; these on bromination and acid cleavage yielded the 4-bromoacetylquinolines. The bromo ketones were then treated with the desired secondary amines, and the intermediate amino ketones were reduced without isolation



The Claisen condensation was found to give excellent yields[10] especially when a considerable excess of sodium ethoxide and ethyl acetate was used. The major trouble encountered in the present work was in the reaction of the bromo ketones with the secondary amines, and the subsequent reduction. It was found necessary to conduct the bromo ketone–amine reaction under anhydrous conditions, in a nitrogen atmosphere, in the absence of light, and at the lowest practical temperature. Unless these conditions were observed the reaction products became a dark red, and poisoned the catalyst in the subsequent hydrogenation. In the case of the compounds reported in this paper catalytic hydrogenation over palladium or platinum was found to be satisfactory, although this method cannot be used with all amino ketones.[11]

In many cases the amino alcohol hydrochlorides were hygroscopic and tended to darken in air. For this reason they were sometimes converted to the more stable and less soluble 1-methylene-bis-(2-hydroxy-3-naphthoates). These were usually obtained as dihydrates.

(8) Lutz, *et al.*, THIS JOURNAL, **68**, 1813 (1946).

(9) (a) Winstein, Jacobs, *et al.*, *ibid.*, **68**, 1831 (1946); (b) Buchman, Sargent, Myers and Seneker, *ibid.*, **68**, in press (1946).

(10) Koelsch, *J. Org. Chem.*, **10**, 39 (1945).

(11) Burger and co-workers, THIS JOURNAL, **60**, 1533 (1938); **65**, 2382 (1943).

Experimental[12]

A. Amino Alcohols Derived from Cinchoninic Acid

The cinchoninic acid was prepared by the method of Ainley and King[13] with certain modifications.

2-Hydroxycinchoninic Acid.—Isatin was acetylated in 75–80% yield by refluxing 100 g. of isatin with 200 ml. of acetic anhydride for two hours. The product, m. p. 143–144°, separated on cooling. It was converted in 77% yield to 2-hydroxycinchoninic acid, m. p. 335–338°, by the method of Ainley and King.[13]

2-Chlorocinchoninic Acid.—Thirty-eight grams of the hydroxy acid and 92 g. of phosphorus oxychloride were heated under reflux at 110–120° for forty-five minutes, and the product worked up in the usual way. The crude material (85–90% yield) was purified through the sodium salt, and then melted at 233–235°.

Cinchoninic Acid.—The following reduction procedure was found more convenient than the one described by Ainley and King.[13] An electrically heated hydrogenation bottle was charged with 20.6 g. of the chloro acid, 12 g. of reagent grade potassium hydroxide pellets, 100 ml. of water and about 3 g. of Raney nickel. The mixture was shaken with hydrogen at 50° and 60 lb. per sq. in. Hydrogenation was complete in forty-five minutes. The yield of cinchoninic acid was 84%. The acid was esterified in the usual way with alcohol and sulfuric acid to give 76% of ethyl cinchoninate, b. p. 120–123° (1 mm.), $n^{20}D$ 1.5846.

Ethyl 4-Quinolylacetate.—Sodium ethoxide was prepared in 50 ml. of dry toluene from 4.1 g. of sodium wire (0.18 mole) and 8.3 g. of absolute[14] ethyl alcohol. Twenty-four grams of ethyl cinchoninate (0.12 mole) and 16 g. of dry ethyl acetate (0.18 mole) were added, and the mixture was stirred at 115° for six hours. The cooled solution was poured into 400 ml. of ice water, the aqueous layer made acid to congo red and extracted with ether. The dried ether solution was saturated with hydrogen bromide to precipitate the keto ester hydrobromide. The yield of product of m. p. 166–168° was 60–70%. This material was converted to 4-bromoacetylquinoline hydrobromide, m. p. 218°, in 73% yield by the method of Rabe.[5]

α-Di-*n*-butylaminomethyl-4-quinoline Methanol.—4-Bromoacetylquinoline hydrobromide (6.6 g., 0.02 mole) was added in the course of twenty minutes to a cold (0°) solution of 10.3 g. of redistilled di-*n*-butylamine in 50 ml. of dry ether, in a nitrogen atmosphere. The mixture was allowed to stand under nitrogen, with occasional shaking, at 0° for five hours. The dibutylamine hydrobromide was removed, the filtrate was evaporated under nitrogen, and the residue was taken up in 100 ml. of methanol containing 4 ml. of concentrated hydrochloric acid. The solution was shaken with hydrogen in the presence of 50 mg. of Adams catalyst until absorption was complete (twenty minutes, 0.02 mole of hydrogen absorbed). The crude product was isolated, and freed from dibutylamine by pumping at 30° and 0.5 mm. It was converted to the dihydrochloride in ether. The yield of salt of m. p. 165° was 28%.

Anal. Calcd. for $C_{19}H_{30}N_2OCl_2 \cdot H_2O$: C, 58.3; H, 8.2; N, 7.1. Found: C, 58.7; H, 8.5; N, 7.4.

The amino alcohol formed a picrate which melted at 110°.

α-Morpholinomethyl-4-quinoline Methanol.—This was prepared as described above, using 2.6 g. of morpholine, 20 ml. of sodium-dried benzene and 3.3 g. of the bromo ketone hydrobromide. The amino ketone was isolated from the benzene solution as the monohydrobromide, which was hydrogenated in aqueous solution in the presence of 0.5 g. of 10% palladium-charcoal. It required ninety minutes for the absorption of 0.01 mole of hydrogen. The amino alcohol was isolated as the monohydrochloride, m. p. 156–160°, in 36% yield.

(12) Most of the analyses reported in this paper were carried out at Columbia University.

(13) Ainley and King, *Proc. Roy. Soc.* (London), **125B**, 60 (1938).

(14) Manske, THIS JOURNAL, **53**, 1106 (1931).

Anal. Calcd. for $C_{15}H_{19}N_2O_2Cl$: C, 61.1; H, 6.49; N, 9.5. Found: C, 61.4; H, 6.0; N, 9.3.

The amino alcohol on treatment with benzoyl chloride formed a benzoate hydrochloride, m. p. 165°, whose free base melted at 114–117°. The amino alcohol picrate melted at 137–139°.

B. Amino Alcohols Derived from Quininic Acid

The quininic acid used in this work was prepared by the general procedure of Ainley and King[13] but several modifications were made which improved the yields and simplified the procedures. These will be described in detail elsewhere. The quininic acid was esterified with ethanol and sulfuric acid to give an 84% yield of the ethyl ester, m. p. 67–68°.

Ethyl 6-Methoxy-4-quinoloylacetate.—The following procedure was found to be better than that of King and Work[7] in which sodamide was used. Thirty-eight grams of ethyl quininate and 21 g. of dry ethyl acetate were added to the sodium ethoxide prepared from 5.5 g. of sodium wire and 11.0 g. of absolute[14] ethanol in 100 ml. of sodium-dried toluene. The mixture was stirred at 110° for ten hours; toward the end of this time the sodium salt of the product separated. The sodium salt was collected, freed from toluene by washing with ether, and dissolved in ice-water. The aqueous solution was acidified to congo paper with hydrochloric acid. The light yellow keto-ester, m. p. 77–79°, was obtained in 75–85% yield. It was converted to the bromo ketone hydrobromide by the method of Rabe[5] in 75% yield.

6-Methoxy-α-diethylaminomethyl-4-quinoline Methanol, SN-2553.[15]—Finely powdered 6-methoxy-4-bromoacetylquinoline hydrobromide (3.6 g., 0.01 mole) was added to a solution of 9 g. of diethylamine in 50 ml. of anhydrous ether at 0°, in an atmosphere of nitrogen, and the mixture was allowed to stand at 0°, with frequent shaking, for two hours. The crude amino ketone was taken up in 100 ml. of 0.5 *N* hydrochloric acid and shaken with hydrogen in the presence of 30 mg. of Adams catalyst until absorption ceased (one hour, 0.009 mole absorbed). The crude amino alcohol was freed from diethylamine under vacuum and precipitated as the dihydrochloride, which was recrystallized from absolute alcohol–ether mixture. The product melted at 170–172° and weighed 2.05 g. (59%). The picrate melted at 177–179°. King and Work,[7] who also prepared this amino alcohol, reported the m. p. of the hydrochloride as 182–183°.

6-Methoxy-α-butylethylaminomethyl-4-quinoline Methanol, SN-9796.—This was made in the same way, using 5.4 g. (0.015 mole) of bromo ketone hydrobromide and 7.6 g. (0.06 mole) of butylethylamine.[16] The amino ketone absorbed 0.014 mole of hydrogen. The dihydrochloride of the product, m. p. 115°, obtained in 50% yield, was converted to the 1-methylene-bis-(2-hydroxy-3-naphthoate) for testing and analysis. This salt, which was a dihydrate, melted at 150–154°.

Anal. Calcd. for $C_{41}H_{42}N_2O_8 \cdot 2H_2O$: C, 67.7; H, 6.4; N, 3.86. Found: C, 67.1; H, 6.0; N, 3.62.

The picrate melted at 157–159°.

6-Methoxy-α-butylpropylaminomethyl-4-quinoline Methanol, SN-7995.—6-Methoxy-4-bromoacetylquinoline hydrobromide (7.2 g.) was allowed to react with 9.2 g. of butylpropylamine[16] at 0° for four hours. The crude amino ketone was reduced in 0.5 *N* hydrochloric acid in the presence of 50 mg. of platinum oxide; the theoretical amount of hydrogen was absorbed in forty minutes. The amino alcohol dihydrochloride, m. p. 169–172°, was obtained in 42% yield.

Anal. Calcd. for $C_{19}H_{30}N_2O_2Cl_2 \cdot H_2O$: C, 56.0; H, 7.9; N, 6.88. Found: C, 55.7; H, 7.3; N, 6.2.

The amino alcohol formed a picrate, m. p. 155–157°, a monohydrochloride, m. p. 140°, and a benzoate hydrochloride, m. p. 157–159°.

6-Methoxy-α-isobutylpropylaminomethyl-4-quinoline Methanol, SN-7997.—A solution of 5.7 g. of 6-methoxy-4-bromoacetylquinoline (free base) in 50 ml. of thiophene-free benzene was added to 5.5 g. of isobutylpropylamine[16] in 30 ml. of benzene, and the mixture was allowed to stand at room temperature for four hours. The amino ketone was hydrogenated in 0.5 *N* hydrochloric acid. The amino alcohol dihydrochloride, m. p. 160°, was isolated in 40% yield, and converted to the 1-methylene-bis-(2-hydroxy-3-naphthoate), which separated as the dihydrate, m. p. 148–150°.

Anal. Calcd. for $C_{42}H_{44}N_2O_8 \cdot 2H_2O$: C, 68.1; H, 6.5; N, 3.8. Found: C, 67.7; H, 6.0; N, 3.6.

C. Amino Alcohols Derived from 6-Chlorocinchoninic Acid

6-Chlorolepidine.—This was prepared from *p*-chloroaniline hydrochloride and 1,3,3-trimethoxybutane by the general procedure of Campbell and Schaffner.[1] The crude product was freed from any primary and secondary amines by treatment with acetic anhydride. The 6-chlorolepidine, obtained in 55% yield, melted at 60° and was satisfactory for use in the next step. A sample recrystallized twice from Skellysolve L, b. p. 98–110°, formed white needles, m. p. 65–66.5°, soluble in alcohol, ether and benzene, fairly soluble in hot petroleum ether.

Anal. Calcd. for $C_{10}H_8NCl$: C, 67.6; H, 4.54; N, 7.9. Found: C, 67.4; H, 4.43; N, 7.6.

6-Chloro-4-styrylquinoline.—A mixture of 98 g. of 6-chlorolepidine, 270 g. of benzaldehyde and 28 g. of anhydrous zinc chloride was stirred at 180° for five hours while water and some benzaldehyde distilled out. The cooled solution was poured into 800 ml. of 5 *N* sulfuric acid, and 200 ml. of ether was added. The mixture was allowed to stand overnight, and the sulfate salt was collected and washed well with ether. It was suspended in 500 ml. of strong sodium hydroxide solution, and the mixture extracted exhaustively with ether. Evaporation of ether gave 134 g. (90%) of the styryl compound, m. p. 82°. Sometimes the crude product was oily, but could be used in the subsequent oxidation. The crude styryl compound darkened in air. A sample of the compound after recrystallization from Skellysolve L, b. p. 98–110°, formed yellow needles, m. p. 88–89°.

Anal. Calcd. for $C_{17}H_{12}NCl$: C, 76.8; H, 4.5; N, 5.27. Found: C, 77.0; H, 4.66; N, 4.72.

6-Chlorocinchoninic Acid.—Powdered potassium permanganate (160 g.) was added in the course of two hours to a solution of 125 g. of the styryl compound in 3 liters of acetone, at 0–10°. The mixture was stirred at 10° for an additional two hours, and filtered. The filter cake was extracted with four 500-ml. portions of boiling water, the extract concentrated to 500 ml. and acidified to congo red. The precipitated acids were thoroughly dried and extracted with ether to remove benzoic acid. There was obtained 90 g. (90%) of 6-chlorocinchoninic acid, m. p. 300–302°. Work[17] reported 302° as the melting point of the acid obtained from 5-chloroisatin. A sample of the crude acid was recrystallized twice from dioxane, and then melted at 304°.

Anal. Calcd. for $C_{10}H_6NO_2Cl$: C, 58.85; H, 2.91; N, 6.75. Found: C, 58.2; H, 2.99; N, 6.65.

Ethyl 6-Chlorocinchoninate.—A mixture of 90 g. of the acid, 450 ml. of absolute alcohol and 72 ml. of concentrated sulfuric acid was refluxed for seven hours. There was obtained a 75% yield of ester, m. p. 68–69° after recrystallization from high boiling ligroin.

Anal. Calcd. for $C_{12}H_{10}NO_2Cl$: C, 61.14; H, 4.28. Found: C, 61.5; H, 4.32.

Ethyl 6-Chloro-4-quinoloylacetate.—This was prepared as described for the 6-methoxy compound, using 10.3 g.

(15) The numbers are those assigned by the Survey of Antimalarial Drugs to identify the drugs in their records. The antimalarial properties of these compounds will be tabulated in a forthcoming monograph.

(16) Campbell, Sommers and Campbell, THIS JOURNAL, **66**, 82 (1944).

(17) Work, *J. Chem. Soc.*, 426 (1942).

of sodium, 200 ml. of toluene, 20.6 g. of alcohol, 40 g. of ethyl acetate and 72 g. of ethyl 6-chlorocinchoninate. The product was recrystallized from ligroin; yield, 65 g., 72%, m. p. 58–60°.

Anal. Calcd. for $C_{14}H_{12}NO_3Cl$: C, 60.6; H, 4.36; N, 5.05. Found: C, 60.9; H, 4.7; N, 5.0.

6-Chloro-4-acetylquinoline.—Six grams of the keto ester was heated with 100 ml. of 15% sulfuric acid until evolution of carbon dioxide ceased. There was obtained 3 g. of ketone as a white, crystalline solid, m. p. 101–103° after recrystallization from high-boiling ligroin.

Anal. Calcd. for $C_{11}H_8NOCl$: C, 64.24; H, 3.92; N, 6.81. Found: C, 64.42; H, 4.10; N, 6.65.

6-Chloro-4-bromoacetylquinoline.—Thirty-two grams of bromine was added dropwise with stirring to 56 g. of the keto ester in 150 ml. of chloroform. The solvent was removed under reduced pressure and 100 ml. of 24% hydrobromic acid was added to the residue. The red solution was warmed gradually to 100° and kept there for one hour. The product suddenly crystallized from the hot solution. 6-Chloro-4-bromoacetylquinoline hydrobromide was isolated in 60 g. (83%) yield as a yellow crystalline powder, m. p. 228–230° (dec.).

Anal. Calcd. for $C_{11}H_8NOBr_2Cl$: C, 36.13; H, 2.21; N, 3.83. Found: C, 36.8; H, 2.38; N, 3.69.

The free base melted at 100–103° and darkened in air.

6-Chloro-α-diethylaminomethyl-4-quinoline Methanol, SN-9209.—Eleven grams of the bromoketone hydrobromide was added to a cold (0°) solution of 11 g. of diethylamine in 75 ml. of anhydrous ether, in a nitrogen atmosphere, and the mixture was kept at 0° for four hours. The crude amino ketone was taken up in 100 ml. of methanol containing 4 ml. of concentrated hydrochloric acid and shaken with hydrogen in the presence of 70 mg. of platinum oxide. The calculated amount of hydrogen was absorbed in thirty minutes. The amino alcohol was isolated as the dihydrochloride dihydrate, m. p. 170–175°, in 32% yield.

Anal. Calcd. for $C_{15}H_{21}N_2OCl_3 \cdot 2H_2O$: C, 46.46; H, 6.50; N, 7.22. Found: C, 46.24; H, 6.5; N, 7.0.

6-Chloro-α-dibutylaminomethyl-4-quinoline Methanol, SN-10513.—This was prepared as described above using 10.3 g. of dibutylamine and 11 g. of the bromoketone hydrobromide. The amino alcohol dihydrochloride monohydrate, m. p. 152–155°, was isolated in 40% yield.

Anal. Calcd. for $C_{19}H_{29}N_2OCl_3 \cdot H_2O$: C, 53.59; H, 7.34; N, 6.58. Found: C, 54.1; H, 7.2; N, 6.4.

Summary

1. Several α-dialkylaminomethyl-4-quinoline methanols derived from cinchoninic acid, quininic acid and 6-chlorocinchoninic acid have been prepared.

2. The preparation of many quinoline derivatives used as intermediates has been described.

NOTRE DAME, INDIANA RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Studies in the Quinoline Series. V. The Preparation of Some α-Dialkylaminomethyl-2-quinolinemethanols[1]

BY KENNETH N. CAMPBELL, CLARENCE H. HELBING[2] AND JAMES F. KERWIN[3]

In view of the fact that some α-dialkylaminomethyl-4-quinoline methanols show antimalarial activity[4] and that the 2- and 4-positions of the quinoline ring are very similar chemically, it was hoped that α-dialkylaminomethyl-2-quinoline methanols might also have antimalarial properties. As no compounds of this type are reported in the literature, we undertook the preparation of some of them. Compounds of the 2-quinoline methanol type with an α-2-piperidyl side chain have, however, been prepared during the general course of the Committee on Medical Research malaria program.[4a]

The original object of the present work was to prepare amino alcohols derived from quinaldic acid, 6-methoxyquinaldic acid and 7-chloroquinaldic acid. The syntheses of the 6-methoxy- and 7-chloro amino alcohols ran into unexpected difficulties, however, and the work was abandoned in favor of more promising compounds. Since several of the intermediates prepared in these series are new compounds, they are reported here.

Quinaldic acid was best prepared in large amounts from quinaldine by way of the α-tribromo derivative, by a modification of the method of Hammick.[5] This method was found to be much superior to oxidation of 2-styrylquinoline or to hydrolysis of 2-cyano-1-benzoyl-1,2-dihydroquinoline prepared by the Reissert reaction[6] on quinoline. Ethyl quinaldate condensed smoothly with ethyl acetate in the presence of sodium ethoxide to give good yields of the keto ester,[7] and the latter was hydrolyzed by dilute acid to 2-acetylquinoline. This ketone was best converted to 2-bromoacetylquinoline by bromination in aqueous hydrobromic acid; bromination in chloroform was less satisfactory. The bromo ketone reacted normally with secondary amines in anhydrous solvents, but it was necessary to exclude light and oxygen[7a] as otherwise the condensation products were tarry and could not be hydrogenated. Hydrogenation of the amino ketones over platinum gave the desired amino

(1) The work reported here was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Notre Dame.

(2) Present address: Armour Research Foundation, Chicago, Illinois.

(3) Present address: Smith, Kline and French Laboratories, Philadelphia, Pa.

(4) King and Work, *J. Chem. Soc.*, 1307 (1940).

(4a) Benson, Bergstrom, Norton and Seibert, THIS JOURNAL, **68**, in press (1946).

(5) Hammick, *J. Chem. Soc.*, **123**, 2883 (1923).

(6) Reissert, *Ber.*, **38**, 1610 (1905); Taylor, *J. Chem. Soc.*, 1110 (1929); Rupe, Paltzer and Engel, *Helv. chim. acta*, **20**, 211 (1937).

(7) Most of the 2- and 4-carbethoxyquinolines give surprisingly good yields in the Claisen condensation; see (a) Campbell and Kerwin, THIS JOURNAL, **68**, 1837 (1946); (b) Koelsch, *J. Org. Chem.*, **10**, 39 (1945).